CSF Evaluation in Neurological Infections

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Conflict of interest NONE

Learning Objectives

- CSF examination is the tool for diagnosis of neurological infections.
- Obtaining CSF through a lumbar puncture is safe and essential.
- CSF findings are the best guide for management.
- There are some contraindications for lumbar puncture in acute neurological infections.

How can a microbe affect CNS function?

- Direct
  - Invasion of parenchyma of brain
    - Viral encephalitis
    - Cerebral abscess
  - Invasion of supporting structures of brain
    - VZV large-vessel vasculopathy

How can a microbe affect CNS function?

- Indirect
  - Immune-mediated CNS damage
    - Acute disseminated encephalomyelitis
  - Infection-triggered metabolic catastrophes
    - Reye's syndrome
  - Toxin-mediated diseases
    - Tetanus
  - Consequence of systemic sepsis
    - Septic encephalopathy

Burden of neurological infection

"rare complications of common infections"

- Cerebral malaria – estimated 445,000 deaths from all malaria / yr*
- Tuberculosis – 1/4 World's pop infected (for which 5-10% lifetime risk of falling ill)*
- Japanese encephalitis – 68,000 cases / yr of which ~30% fatal*
- Measles – estimated 89,789 deaths globally yr*
- Rabies – estimated 55,000 deaths / yr worldwide & 15 million post-exposure treatments*
- Tetanus – 49,000 deaths in <5 years old worldwide*
- Leprosy – in 2012 173,358 new cases worldwide (reduced from 804,000 in 1998)*

*Source: WHO website – data for 2015; accessed Jan 2014

Classes of organisms causing CNS infections

- Viruses – multiple: DNA & RNA
- Bacteria – aerobic & anaerobic
- Fungi & yeasts – e.g. *Cryptococcus neoformans*
- Protozoa – e.g. *Toxoplasma gondii, Naeglera spp,* trypanosomes & malaria
- Helminths (worms) – e.g. *Taenia solium* & *Echinococcus granulosus*

How do CNS infections cause damage?

- Vicious cycle
  - Microbial invasion causes inflammatory response
    - Blood brain barrier breakdown
    - Cytokine release
    - Endarteritis & microvascular thrombosis
      (e.g. bacterial meningitis)
  - Raised ICP
    - Vasogenic, interstitial & cytotoxic cerebral oedema
  - Direct neuronal injury
    - Resulting in neuronal necrosis or apoptosis

Neuroinfection Syndromes

- Acute:
  - Meningitis (Enterovirus, mumps & HSV-2)
  - Ventriculitis (CMV in immunosuppressed)
  - Encephalitis (including arboviral)
  - Myelitis (e.g. poliomyelitis, JE, WNE, & Rabies)
  - Radiculitis & ganglionitis
    (e.g. shingles, Bell's palsy)

Neuroinfection Syndromes

- Subacute & chronic
  - Subacute sclerosing panencephalitis (measles)
  - Progressive multifocal leucoencephalopathy
    - Human polyoma virus JC
  - HIV dementia (HIV Neurocognitive disorders – HAND)
  - Tropical spastic paraparesis (HTLV-1)

Diagnosis of Neurological Infection

- The neurological formulation:
  - Anatomy
  - Pathogenetic mechanism
  - Aetiology
- The ID mantra:
  - Why did this person?
  - From this place?
  - At this time, get this disease?

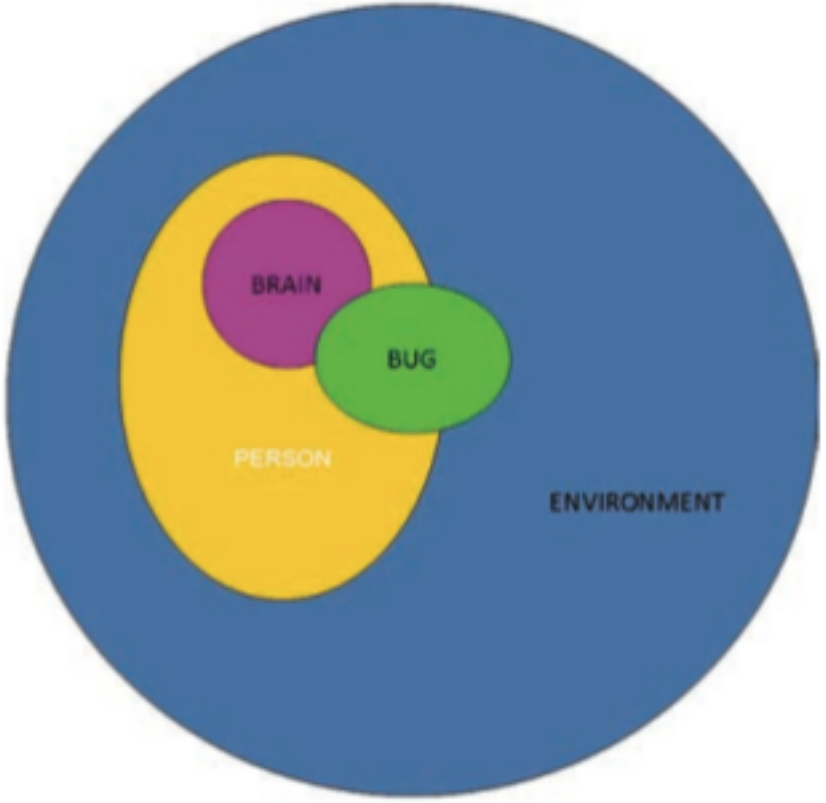


Figure 1 The biology of nervous system infectious diseases.

THE BARE ESSENTIALS Infections of the nervous System. Practical Neurology 2011;11:121–131

Acute Infectious Meningitis

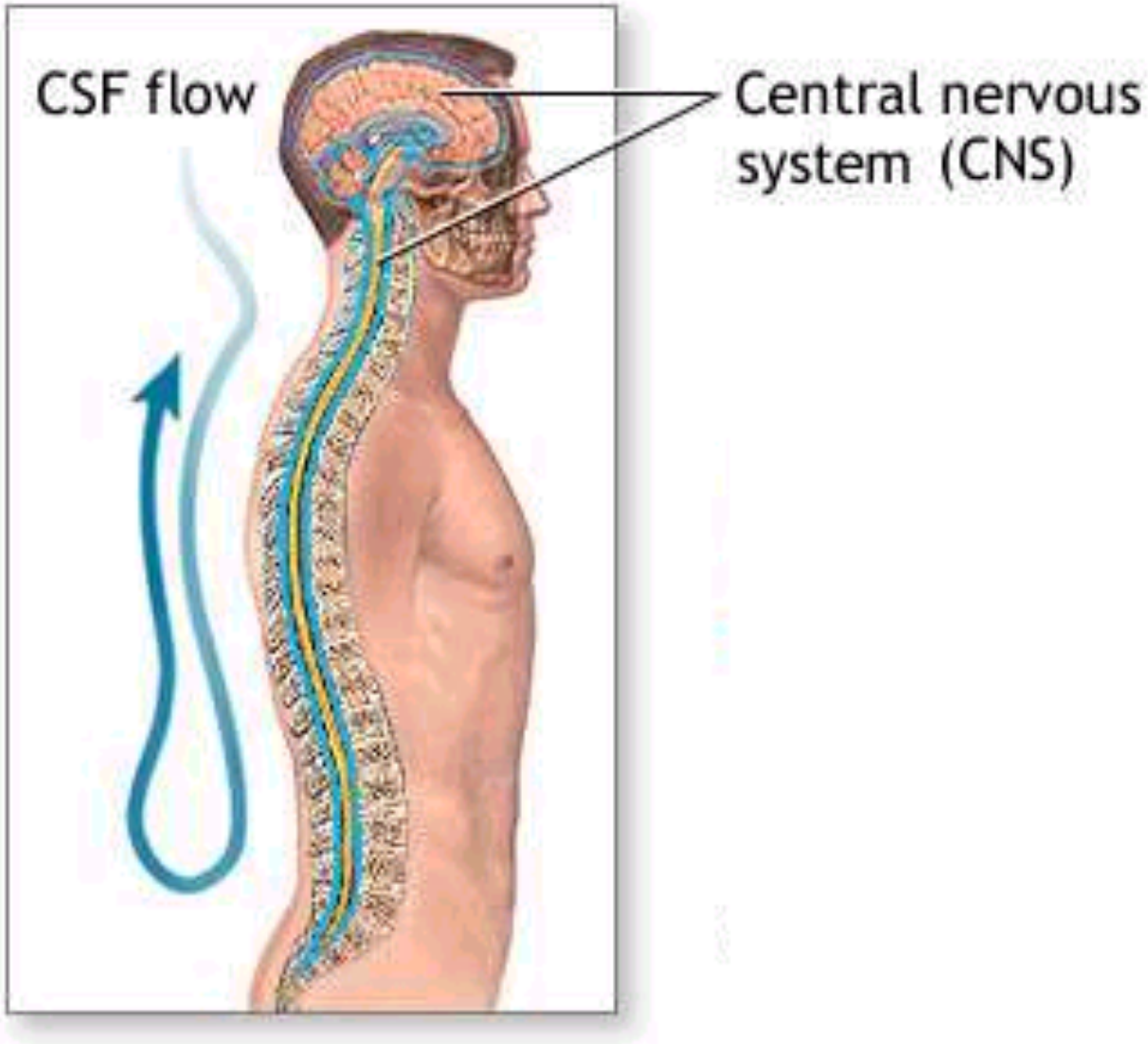
- Viral causes
  - Incidence ~11 / 100,000 / year
  - Common aetiologies:
    - Enteroviruses (85-95% cases)
    - Herpes simplex virus type-2
    - Mumps (n.b. current epidemic amongst those born between 1982-1990)
  - Predominantly children & young adults
  - Usually benign & only requiring symptom relief

Acute Infectious Meningitis

- Bacterial causes
  - Incidence 3-5 / 100,000 / year
  - Aetiologies accounting for 85% cases:
    - *Neisseria meningitidis* (Meningococcus)
    - *Streptococcus pneumoniae* (Pneumococcus)
    - *Haemophilus influenzae*
    - Rarer causes include Listeria, *E. coli,* TB, *Strept suis*
  - Different organisms in different age groups
  - High morbidity & mortality

Investigation of suspected CNS infections

- Anatomy – *imaging techniques & EEG*
- Pathology & aetiology – *analysis of CSF*
- Contraindications to LP (without imaging):
  - Reduced level of consciousness
  - Focal neurological signs
  - Immunosuppression
  - Papilloedema
  - Anticoagulation / bleeding disorder
    - Nb not corrected by imaging!


CSF flow
Central nervous system (CNS)

Risk Factors for Cerebral Herniation Following Lumbar Puncture for Bacterial Meningitis[a]

Clinical Risk Factors

- Stupor or coma
- Dilated or fixed pupils
- Fixed deviation of eyes or absent oculocephalic reflex
- Papilledema
- Recent seizures
- Decorticate or decerebrate posturing
- Hemiparesis
- Hypertension with bradycardia

CT Factors for Increased Risk of Future Brain Herniation

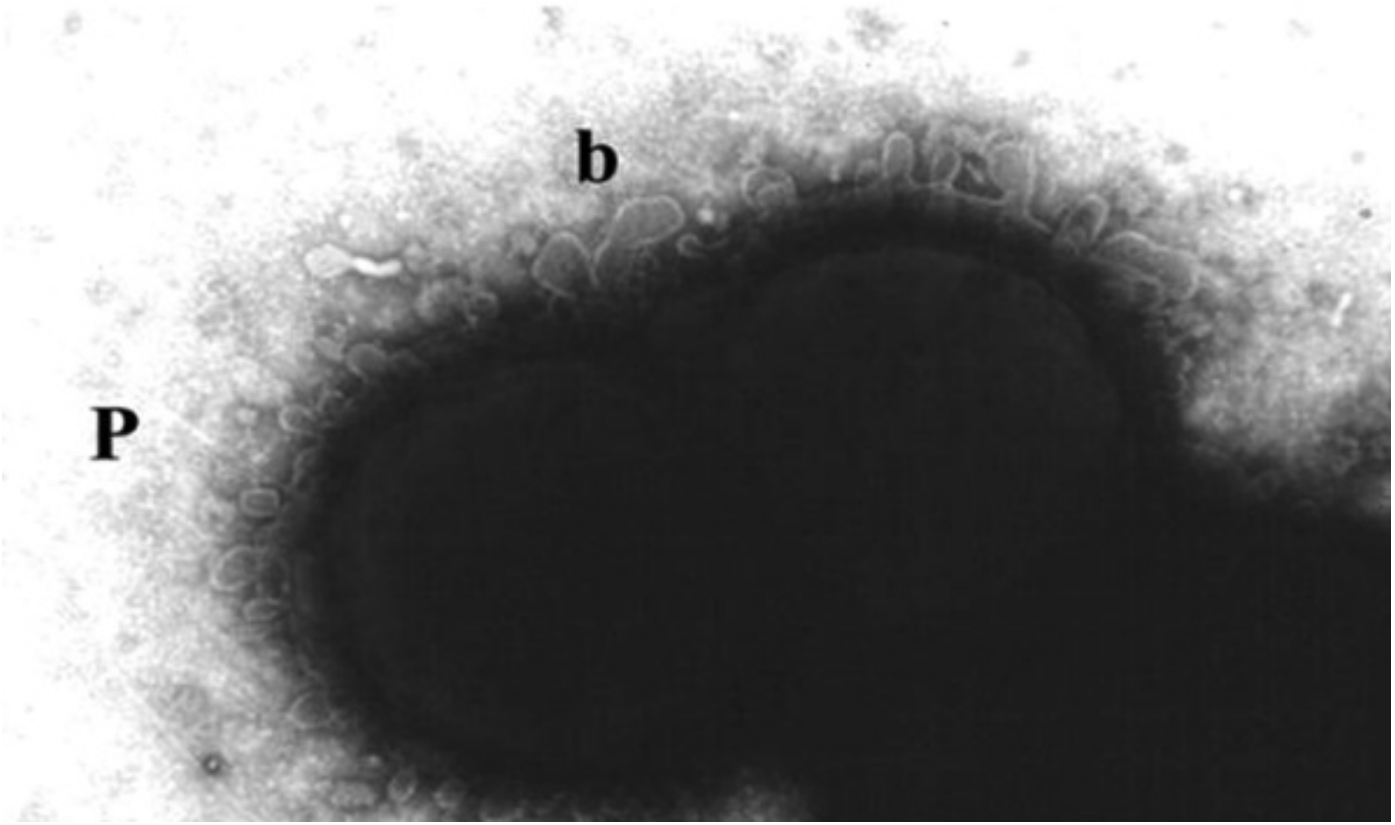
- Lateral shift of cerebral midline structures indicating unequal supratentorial intracranial pressure
- Loss of suprachiasmatic and basilar cisterns indicating the supratentorial pressure is greater than infratentorial; the lateral ventricles may be either large or small
- Obliteration or shift of the fourth ventricle indicating increased posterior fossa pressure
- Obliteration of the superior cerebellar and quadrigeminal plate cisterns with sparing of the ambient cisterns indicating upward cerebellar transtentorial herniation
- Masses in the cerebral hemisphere or cerebellum
- Infarction or occlusion of the superior sagittal sinus or draining veins

Davis LE, Continuum, Neuroinfectious Diseases; Acute Bacterial meningitis 2018:1264-83.

CSF Tests

- Cell count & cytology
  - Mononuclear vs polymorphs
- Gram stain (60-90% +ve)
- Antigen detection (e.g. Cryptococcus)
- Microbial culture
  - for pyogenic bacterial meningitis
    - Pre-antibiotics 70-85% +ve & post-antibiotics 50%
  - Low sensitivity for viruses
- CSF/plasma glucose or CSF lactate
    - CSF [lactate] >3.5 mmol/L
- Nucleic acid detection (PCR)
    - For meningococcus ≈91% sensitivity & specificity
    - Standard for many viruses
- CSF antibody tests

Fig 2 Electronmicrograph showing blebbing (b) of the outer membrane of Neisseria meningitides



Hart, C A. et al. BMJ 2006;333:685-690

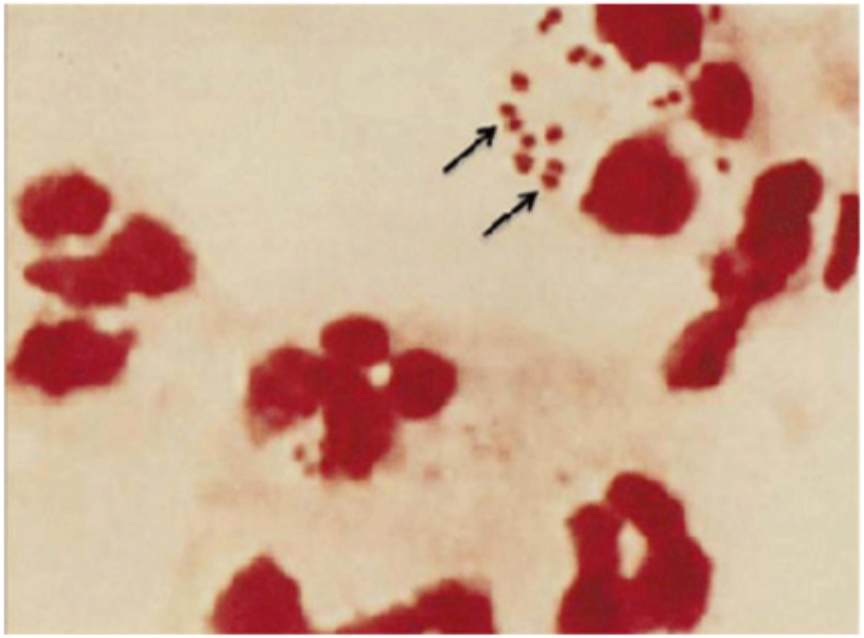


Figure 1. Gram stain of *N. meningitidis* in CSF with associated PMNs.

N. meningitidis may occur intracellularly or extracellularly in PMN leukocytes and will appear as gram-negative, coffee-bean shaped diplococci.

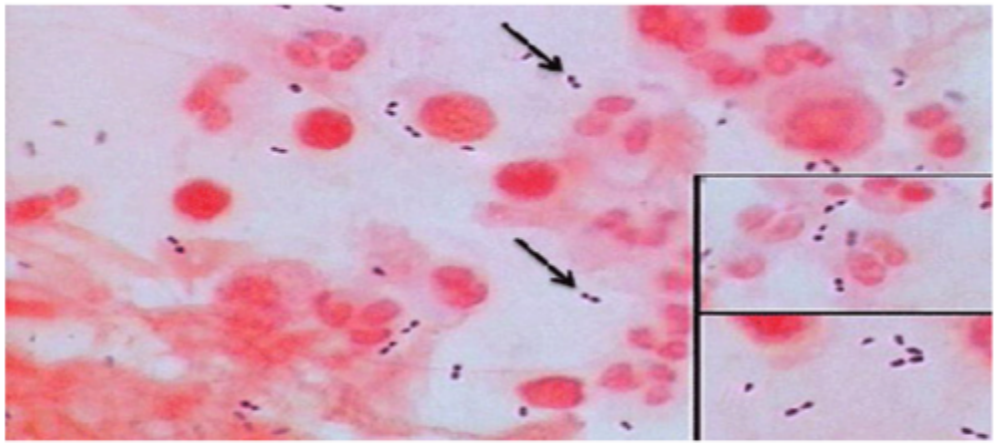


Figure 2. Gram stain of *S. pneumoniae* with WBCs

S. pneumoniae may occur intracellularly or extracellularly and will appear as gram-positive, lanceolate diplococci, sometimes occurring in short chains.

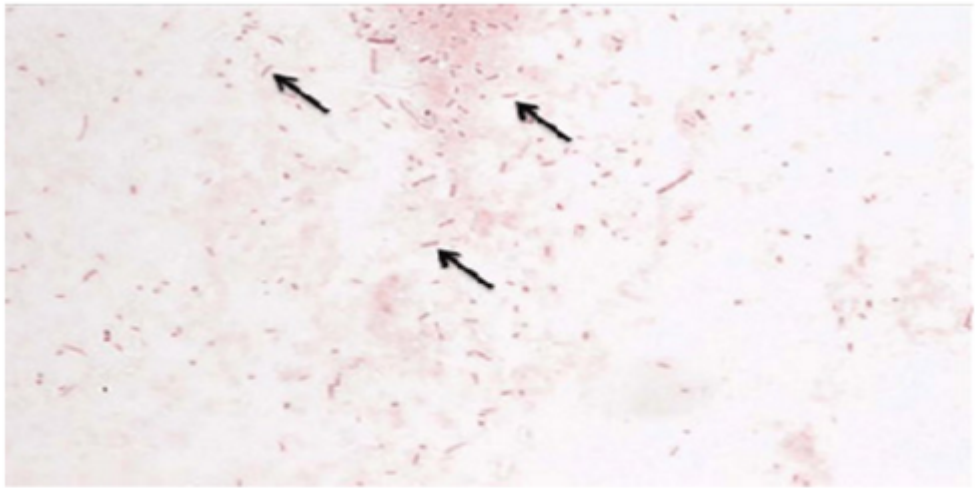
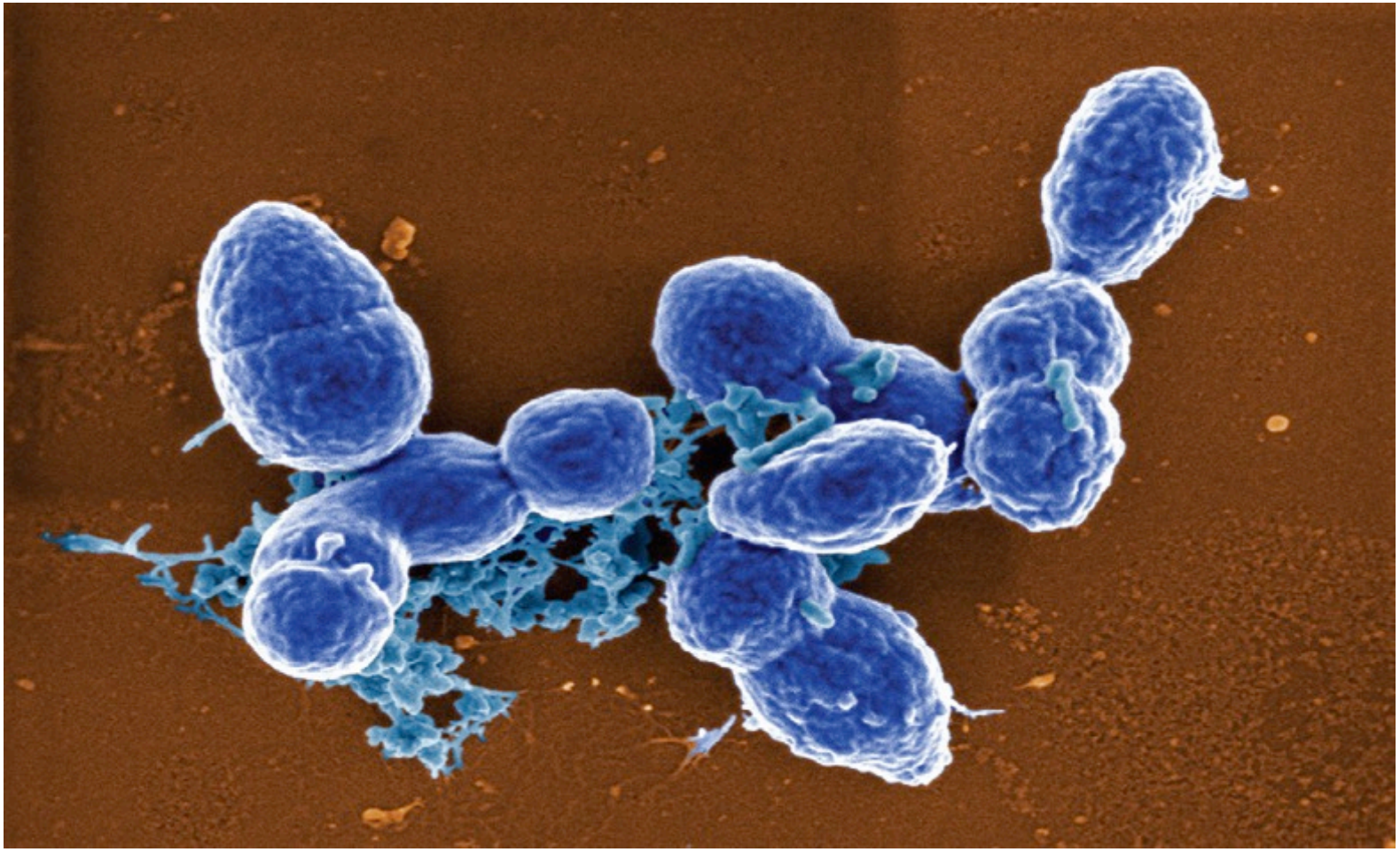


Figure 3. Gram stain of *H. influenzae*

H. influenzae are small, pleomorphic gram-negative rods or coccobacilli with random arrangements.

Gram Stain available in 4hrs
60-90% Number of organisms

Common causes of Community Acquired BM are *S pneumoniae and N menigitides*



Coloured Scanning electron micrograph of *streptococcus pneumoniae*
Van de Beek Lancet 2012; 380:1703

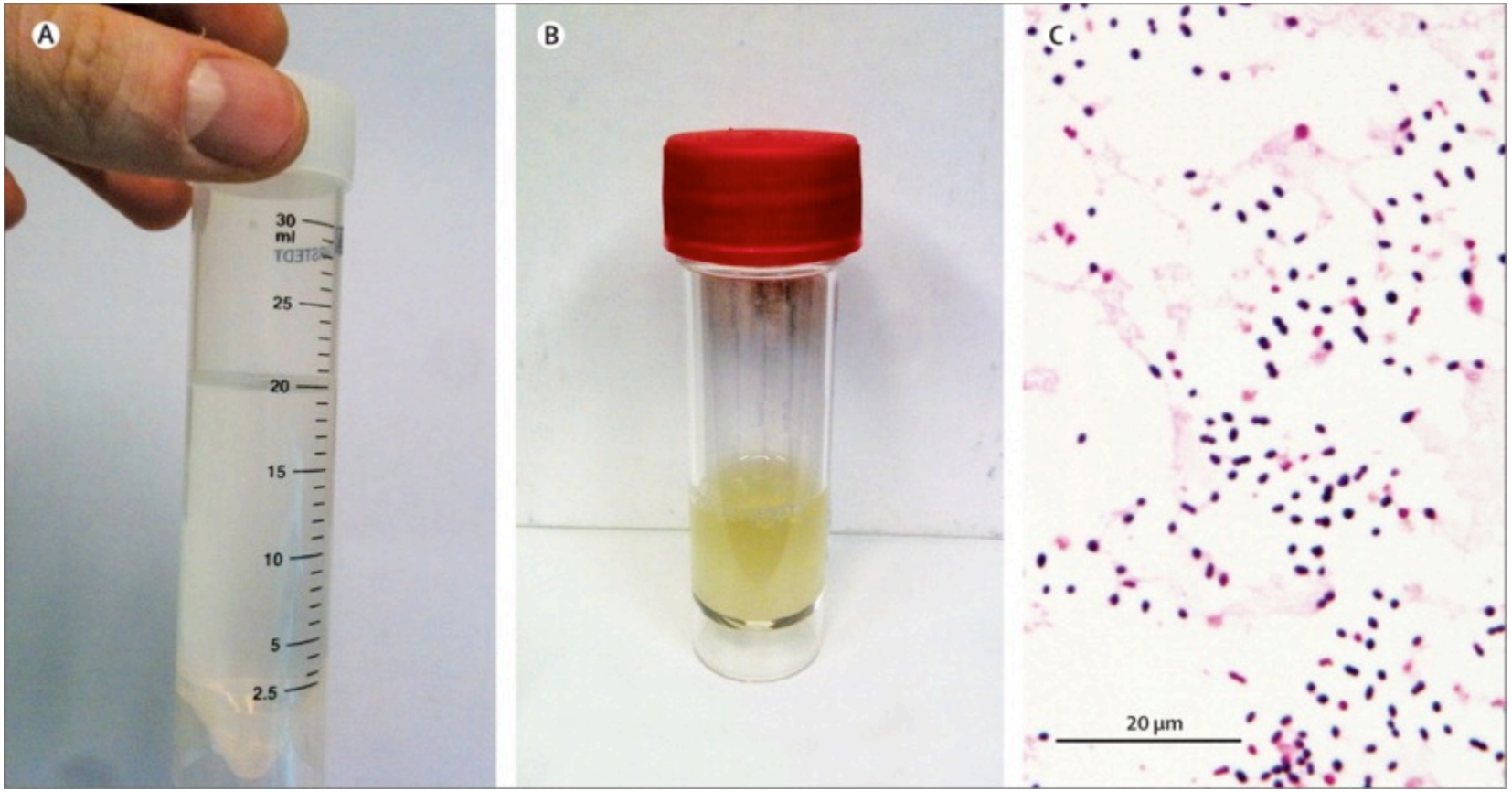
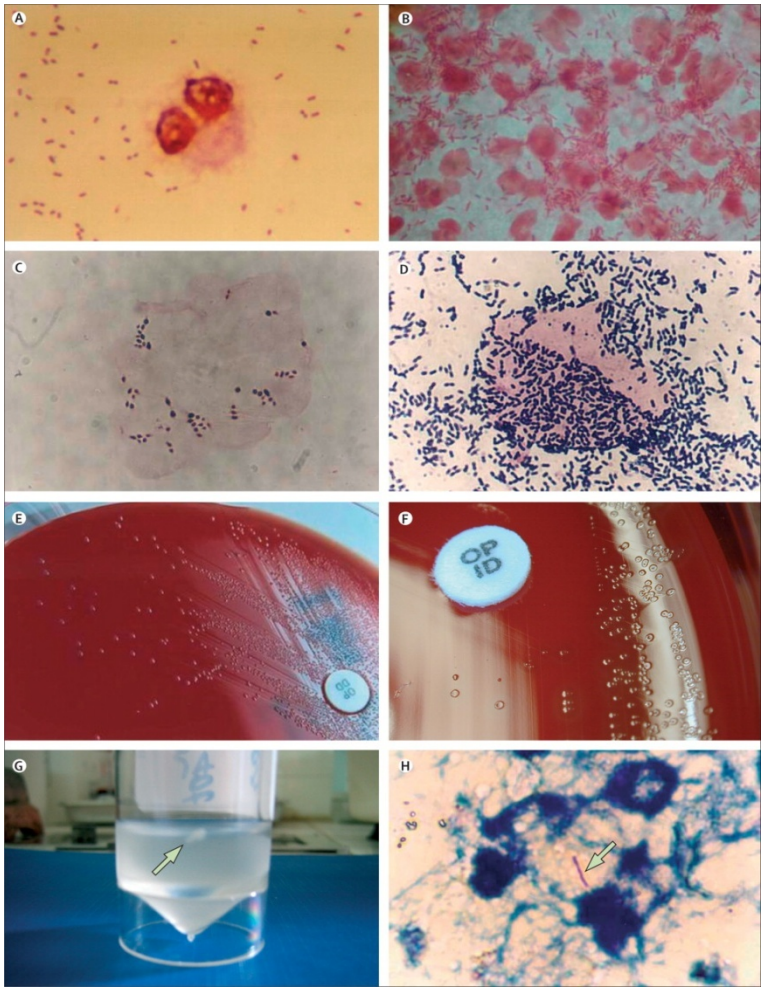


Fig 2: Cerebrospinal Fluid appearances in bacterial meningitis
(A) Normal CSF. (B) Yellow trubid CSF. (C) CSF Gram-positive diplococci (*Streptococcus pneumoniae)* Brouwer et al Lancet 2012;380:1684-92.



A. Gram + diploccoci S pnumoniae
B. Neutrophils G – rods **E coli**

C. CSF intracellular G+ cocci *S suis*
D. Skin G+ *S pneumonie*

E. Optochin Disc diffrentiate *S pneumoniae*
F. Optochin Senstive *S pneumoniae*

G. Spider web Pro>1.5 gm/L
H. ZN stain Single AFB

Scarborough&Thwaites Lancet Neurol 2008;7:637-648

Table 4 Classical CSF Features of the different causes of meningitis.

	Normal	Bacterial	Viral	Tuberculous	Fungal
Opening Pressure (cm CSF)	12–20	Raised	Normal/mildly raised	Raised	Raised
Appearance	Clear	Turbid, cloudy, purulent	Clear	Clear or cloudy	Clear or cloudy
CSF WCC (cells/uL)	<5	Raised (typically >100)[a]	Raised (typically 5–1000)[a]	Raised (typically 5–500)[a]	Raised (typically 5–500)[a]
Predominant cell type	n/a	Neutrophils[b]	Lymphocytes[c]	Lymphocytes[d]	Lymphocytes
CSF protein (g/L)	<0.4	Raised	Mildly raised	Markedly raised	Raised
CSF glucose (mmol)	2.6–4.5	Very low	Normal/slightly low	Very low	Low
CSF/plasma glucose ratio	>0.66	Very low	Normal/slightly low	Very low	Low

CSF – cerebrospinal fluid; WCC – white cell count.
Local laboratory ranges for biochemical tests should be consulted and may vary from these quoted here.
A traumatic lumbar puncture will affect the results by falsely elevating the white cells due to excessive red cells. A common correction factor used is 1:1000.

[a] Occasionally the CSF WCC may be normal (especially in immunodeficiency or tuberculous meningitis).

[b] May be lymphocytic if antibiotics given before lumbar puncture (partially treated bacterial meningitis), or with certain bacteria e.g. *Listeria monocytogenes*.

[c] May be neutrophilic in enteroviral meningitis (especially early in disease).

[d] May be neutrophils early on in the course of disease.

TABLE 7-3 Cerebrospinal Fluid Diagnostic Studies for Meningitis

- **Cell Count With Differential**
- **Glucose and Protein Concentration**
- **Stain and Culture**

  Gram's stain and bacterial culture

  India ink and fungal culture

  Viral culture

  Acid fast smear and *Mycobacterium tuberculosis* culture
- **Antigens/Antibodies if Fungal Meningitis Is in the Differential**

  Cryptococcal polysaccharide antigen

  Histoplasma polysaccharide antigen

  Coccidioides immitis complement fixation antibody

- **Polymerase Chain Reaction (PCR)**
  - Broad range bacterial (16S ribosomal DNA) — Takes 48hrs
  - Specific meningeal pathogen
    - Reverse transcriptase for enteroviruses — Takes 4hrs
    - Herpes simplex virus type 1 and type 2
    - West Nile virus
    - Epstein-Barr virus
    - Varicella-zoster virus
    - NAAT for *M. tuberculosis* — Nucliec acid amplification test — Modified ZN stain
    - Human immunodeficiency virus (HIV) RNA
- **Antibodies**
  - Herpes simplex virus (serum and CSF IgG to calculate antibody ratio)
  - Varicella-zoster virus IgM and IgG antibody index
  - Arthropod-borne viruses (West Nile virus IgM)
  - *Borrelia burgdorferi* antibody index

CSF = cerebrospinal fluid; DNA = deoxyribonucleic acid; IgG = immunoglobulin G; IgM = immunoglobulin M; NAAT = nucleic acid amplification test; RNA = ribonucleic acid.

Accuracy of CSF results to differentiate bacterial meningitis , in case of negative gram-stained smear
Ray et al Am J Emerg Med 2007;25:179-184

- CRP, PCT, CSF WCC, absolute Neurtrophil count and CSF/blood glucose, CSF protein, levels were significantly higher in the BM group.
- However, as a diagnostic indicators of BM, none of these variables except PCT was more efficient that the emergency physician.
- CSF results have a modest role in distinguishing BM from NBM in a negative gram stain for bacteria.
- PCT serum levels seem to be an excellent predictor of BM.

Box 4. Risk factors for a fatal outcome in meningococcal disease.

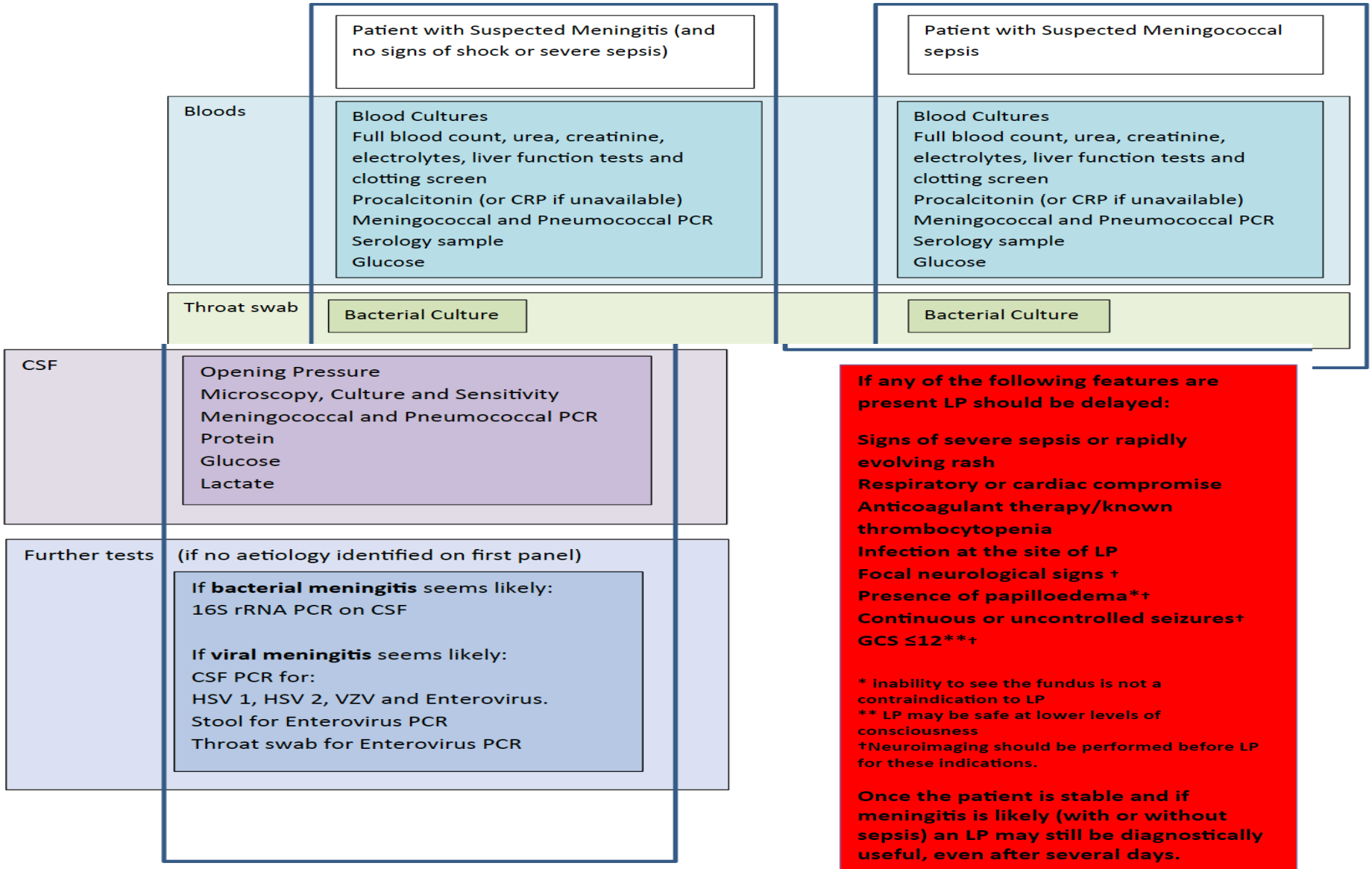
Rapidly progressing rash
Coma
Hypotension and shock
Lactate >4 mmol/L
Low/normal peripheral white blood cell count
Low acute phase reactants
Low platelets
Coagulopathy
Absence of meningitis

Table 1 Description of the FOUR and GCS scores

	FOUR score	GCS score
Eye response	4. Eyelids open or opened, tracking or blinking to command 3. Eyelids open but not tracking 2. Eyelids closed but open to loud voice 1. Eyelids closed but open to pain 0. Eyelids remain closed with pain	4. Eyes open spontaneously 3. Eyes open to verbal command 2. Eyes open to pain 1. No eye opening
Motor response	4. Thumbs-up, fist, or peace sign 3. Localizing to pain 2. Flexion response to pain 1. Extension response to pain 0. No response to pain or generalized myoclonus status	6. Obeys commands 5. Localizing pain 4. Withdrawal from pain 3. Flexion response to pain 2. Extension response to pain 1. No motor response
Brainstem reflexes	4. Pupil and corneal reflexes present 3. One pupil wide and fixed 2. Pupil or corneal reflexes absent 1. Pupil and corneal reflexes absent 0. Absent pupil, corneal, and cough reflex	
Respiration	4. Not intubated, regular breathing pattern 3. Not intubated, Cheyne-Stokes breathing pattern 2. Not intubated, irregular breathing 1. Breathes above ventilator rate 0. Breathes at ventilator rate or apnea	
Verbal response		5. Oriented 4. Confused 3. Inappropriate words 2. Incomprehensible sounds 1. No verbal response

Abbreviations: FOUR = Full Outline of Unresponsiveness; GCS = Glasgow Coma Scale.

Van Ettekoven et al Neurology 2019



PCR-Polymerase Chain Reaction; CSF – cerebrospinal fluid; HSV – herpes simplex virus; VZV – varicella zoster virus; LP – lumbar puncture; CRP – C-reactive protein; GCS – Glasgow Coma Scale; rRNA – ribosomal ribonucleic acid

Figure 1 Investigations algorithm.

Bacterial Infections of the Central Nervous System

Karen L. Roos, MD, FAAN

"The evidence supports the use of dexamethasone at the initiation of therapy and for the first 4 days".

The identification of and eradication of the pathogen with antimicrobial therapy is the easy part.
It is the recognition of the disorder, the understanding of which diagnostic studies to obtain and their limitations, and the management of the neurologic complications that require the expertise of a neurologist.

Continuum (Minneap Minn) 2015;21(6):1679–1691.

ccuracy of Cerebrospinal Fluid Biochemical Analysis in Patients With Suspected Bacterial Meningitis

Table 4. Accuracy of Cerebrospinal Fluid Biochemical Analysis in Patients With Suspected Bacterial Meningitis

CSF Test	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)
White blood cell count ≥500/μL[56]	15 (10-22)	0.30 (0.20-0.40)
Glucose >39.6 mg/dL (>2.2 mmol/L)[56]	23 (13-40)	0.50 (0.40-0.60)
Blood glucose ratio ≤0.4[56]	18 (12-27)	0.31 (0.21-0.45)
Blood glucose ratio <0.4		
Briem,[57] 1983*	145 (20.4-1029)	0.25 (0.15-0.40)
Lactate >27 mg/dL (>3 mmol/L)		
Komorowski et al,[58] 1986	2.9 (2.4-3.5)	0.20 (0.06-0.50)
Lactate ≥31.5 mg/dL (≥3.5 mmol/L)		
Lannigan et al,[55] 1980	13 (8.6-20)	0.20 (0.06-0.50)
Lindquist et al,[56] 1988	25 (16-38)	0.12 (0.06-0.20)
Briem,[57] 1983†	38 (15-94)	0.01 (0.001-0.20)
Summary	21 (14-32)	0.12 (0.07-0.23)

Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid.
*n = 245.
†n = 218.

Straus, S. E. et al. JAMA 2006;296:2012-2022.

Key message and conclusions

- Infection can cause CNS dysfunction in a variety of ways.
- Neurological infections may not be common but have high morbidity & mortality. The economic burden of these diseases is considerable.
- Examining the CSF is the crucial procedure.
- Early treatment is essential for optimum outcome.

Resources

-Solomon, T., Michael, B.D., Smith, P.E., *et al. Management of suspected viral encephalitis in adults - Association of British Neurologists and British Infection Association National Guidelines. Journal of Infection 64, 347-373 (2012).*
-Neuroinfectious diseases. Continuum American Academy of Neurology 2018, Vol24.No5.
-McGill etal Acute bacterial meningitis in adults. Lancet 2016;388:3036-47.
Houlihan CF, Bharucha T, Breuer J. Advances in molecular diagnosis testing for central nervous system infections. Curr Opinion 2019 Walter Kluwer Health Vol 32,Number 3:244-50.
-Brouwer MC, van de Beek D, Epidemiology of community acquired bacterial meningitis. Curr Opinion 2018 Walter Kluwer Health Vol31;Number1.
-Donovan et al. The neurocritical care of tuberculous meningits. Lancet Neurol 2019:18:771-83.
-Van Ettekoven et al. The FOUR score as predictor of outcome in adults with bacterial meningitis. Neurology 2019;92:e2522-2526.
-Kneen, R., Michael, B.D., Menson, E., *et al. Management of suspected viral encephalitis in children - Association of British Neurologists and British Paediatric Allergy, Immunology and Infection Group national guidelines. J Infect 64, 449-477 (2012)*
-McGill et al The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults. J Infection 2016;72:405-438

Further Reading & References (2)

Further papers (to those referenced already):

Tyler KL. Acute Viral Encephalitis. N Engl J Med. 2018 Aug 9;379(6):557-566.

Dalmau J, Graus F. Antibody-Mediated Encephalitis. N Engl J Med. 2018 Mar1;378(9):840-851

Tyler Emerging viral infections of the central nervous system parts 1 & 2 *Archives of Neurology* 2009; 66: 939-948 & 66: 1065-1074

Davies & Thwaites Infections of the nervous system. *Pract Neurol* (2011); 11:121-131.

van de Beek, D et al. *Adjunctive dexamethasone in bacterial meningitis: a meta-analysis of individual patient data. Lancet Neurol* (2010); 9: 254-263.